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Application No.	PCT/IE99/00037
Date of Filing	7 May 1999
Applicant	SALVIAC LIMITED, an Irish company of 39-40 Upper Mount Street, Dublin 2, Ireland.

Dated this 17 day of August 2001.

An officer authorised by the
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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

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International Application No. PCT/IE 99/00037

International Filing Date 07 MAY 1999 (07.05.99)

IRISH PATENTS OFFICE PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) SALV12/C/WO

Box No. I TITLE OF INVENTION

"Biostable Polyether Polyurethane Product"

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SALVIAC LIMITED
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☐ This person is also inventor.

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Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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County Roscommon
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This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

O'BRIEN, John A; WELDON, Michael J,
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Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Moone
Athy
County Kildare
Ireland

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CANNON, Ann Marie
Main Street
Pettigo
County Donegal
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

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This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

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This person is applicant for the purposes of:
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

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This person is applicant for the purposes of:
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Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

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- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
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- ☒ DE Germany ..and utility model
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

PCT/EP 99/00031

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	4
description (excluding sequence listing part)	:	11
claims	:	7
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	23

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: 39802 , 40018
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

John O'Brien

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1. Date of actual receipt of the purported international application:	07 MAY 1999 (07.05.99)	2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA / EP	6. ☐ Transmittal of search copy delayed until search fee is paid.	

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"BIOSTABLE POLYETHER POLYURETHANE PRODUCTS"

This invention relates to biostable biocompatible polyether products suitable for long term implantation within a living human body and as a suitable substratum for cell growth technologies.

Background of the Invention

Extensive investigations have been undertaken over many years to find materials that will be biologically and chemically stable towards body fluids and body tissue. This area of research has become increasingly important with the development of various objects and articles which can be implanted into a living body, such as pacemaker leads, vascular grafts, mammary prostheses, pacemaker bodies, probes, catheters and the like. Polyurethanes have become crucial to many of these devices.

Flexible polyurethane foams have been manufactured for more than thirty years from polyisocyanates and polymeric polyols. They have been used in the production of elastomers, flexible and rigid foams, coatings, adhesives and many other products in the industrial sector. The most commonly used polyisocyanate has been TDI (Toluene Diisocyanate) but in recent years this has been replaced with MDI (Diphenylmethane Diisocyanates). Isocyanate polyurethane prepolymers obtained by reacting a stoichiometric excess of a polyisocyanate with an organic polyol are well known in the field of polyurethanes.

The production of foamed materials based on polyurethane and other polymer systems derived from organic polysiloxanes in industrial applications is also well established. The formulation and processing conditions used during manufacture affects the properties of the foam product. They can vary in texture from soft flexible foams used in cushioning applications to hard rigid materials used as

insulating or structural materials. The density and strength of the material can also be affected by the formulation.

It is the objective of the present invention to provide a resilient but soft, flexible polyether polyurethane material that is three dimensional and crosslinked at a molecular level. These properties make the material suitable for long term implantation and cell growth technologies.

While there are some polymeric materials available for use in medical implant technologies there is a need for improved polymeric materials for such applications.

Statements of Invention

The invention provides a resilient but soft, flexible polyether polyurethane material that is three dimensional and crosslinked at a molecular level. These properties make the material suitable for long term implantation and cell growth technologies.

According to the invention there is provided a biostable polyether polyurethane article comprising a medical implant and or a substratum for tissue and/or cell growth formed from an organic diisocyanate, a polyether polyol, a chain extender and a blowing agent.

Most preferably the blowing agent is water.

In a particularly preferred embodiment of the invention the density of the article is less than 1200kg/m^3. Ideally, the density of the article is less than 200kg/m^3.

The ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyether polyurethane biomaterial.

The article may be processed by a metering and mixing process, wherein the chemical components are aggressively mixed and dispensed into a vessel and chain extension and blowing reactions occur substantially simultaneously.

In one case the article is processed by a reactive moulding process, wherein the chemical components are mixed and dispensed into a vessel wherein chain extension occurs.

The article may be processed in two stages, a first stage involving a reaction process in which the number of isocyanate linkages in the reaction vessel is approximately equal to the number of active hydrogens in the vessel, the resulting material being further processed into desired geometries using thermomechanical and/or solvent based processes.

The article may also be processed by a reactive blowing process, in which the chemical components are aggressively mixed and dispensed substantially continuously and expand and chain extend substantially simultaneously to form a continuous block of foam which is subsequently cut or machined into a desired geometry.

Most preferably the density of the said article is controlled by controlling the pressure in the reaction vessel.

Ideally the article has a pore size of from 10 microns to 900 microns, most preferably from 35 microns to 200 microns.

In one aspect the invention provides a biostable polyether polyurethane wherein the urea linkages are derived from a water isocyanate reaction present in the hard segment phase. Preferably the percentage of urea linkages in the hard segment phase is greater than 0.5%.

In another aspect the invention provides a biostable polyether polyurethane wherein biuret linkages exist in the hard segment phase.

In a further aspect the invention provides a biostable polyether polyurethane wherein aliphatic linkages exist in the hard segment phase.

Further details of the invention are given in claims 17 to 46.

Detailed Description

The biostable polyether polyurethane devices of this invention are derived from organic diisocyanates and polyether polyols, polyether copolymer polyols or combinations thereof and are chain extended with either diamine, diol, water or mixtures of the above chain extenders. The reaction step converts the chemical precursors into a 3 dimensional molecular cross-linked structure, simultaneously forming a low density porous material. A 3 dimensional network of this kind is insoluble and intractable. Manufacturing the article by this method produces a material with minimal internal stress, enhancing biostability.

Altering the chemical precursors and the processing conditions of the material may alter the pore size and the density of the material, as required, to meet the requirements of the application.

The biostable polyurethanes of this invention are useful for the manufacture of catheters, vascular grafts, septal occluders, vessel occluders, embolisation devices,

mammary prosthesis, pacemaker leads and other such implant, blood contacting devices and as cell scaffolds to support cell growth.

The biostable polyurethanes of this invention are based on organic diisocyanates, polyether copolymer polyols, polyether homopolymers and diol, diamine or water chain extenders and combinations thereof. The product of this invention relates to a liquid isocyanate – containing prepolymer composition with an average functionality of 2.

The product of this invention has applications in the medical device and tissue engineering sectors, however the material can also be used as a cell scaffold to support cell growth.

Details on the chemistry of the invention are as follows;
The organic diisocyanates are of the general formula:
$R-(NCO)_n$

R is an aliphatic, aromatic, cycloaliphatic, or an aliphatic-aromatic hydrocarbon entity containing between 4 and 24 carbon atoms and "n" varies between 1.85 and 3. More preferably, R contains between 4 and 13 carbon atoms. Where n is 2, a polymer with a linear molecular structure may be produced. A three dimensional molecular network may be produced where n varies from 1.85 to 3. Ideally n should be between 1.9 and 2.2.

Examples of suitable isocyanates include: p-phenylene diisocyanate, tetramethylene diisocyanate, cyclohexane 1, 2-diisocyanate, m-tetramethylxylene diisocyanate, hexamethylene diisocyanate, 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, and mixtures of the above.

More ideally the following isocyanates can be used to manufacture suitable materials; 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, and mixtures of the above.

Even more ideally, the following diisocyanates can be used to manufacture suitable polyurethanes: 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 4,4 -dicyclohexylmethane diisocyanate.

Polyether polyols that may be used include products obtained by the polymerisation of cyclic oxide, for example, ethylene oxide, propylene oxide, butylene oxide, or tetrahydrofuran in the presence of polyfunctional initiators. Suitable initiator compounds contain plurality of active hydrogen atoms including water and polyols, e.g., polyethylene glycol, polypropylene glycol, polydiethylene-ether glycol or polycaprolactone glycol.

Useful polyether polyols include polytetramethylene glycols. The polytetramethylene glycols used in this invention having varying molecular weights of between 600 and 3000. Polyols of differing molecular weights can be used together in a single formulation.

The polyether polyurethanes of this invention are based on diol, diamine, alkanolamine, water chain extenders or mixtures of these. Diol chain extenders react with isocyanate to generate urethane linkages. Diamine and water generate urea linkages and alkanol amines can generate both urethane and urea linkages. The use of water as a chain extender in low density, three dimensional biomedical polyurethanes is unusual as with most conventional biomedical polyurethanes water is viewed as an impurity. The water chain extension reactions generate urea linkages in the hard segment and carbon dioxide is given off as a by-product.

The presence of significant quantities of urea linkages in the hard segment has the following important effects:

- Polyureas in the hard segment generate significant levels of hydrogen bonding that causes the hard segment to be strong and this adds to the ultimate properties of the material.
- It also promotes phase separation of the hard isocyanate/chain extender phase and the soft polyol phase. Phase separation is beneficial to the elastomeric and biocompatibility properties of the material.
- The presence of significant concentrations of urea linkages in the hard segment make linear polyurethanes difficult to process by thermomechanical techniques.
- The carbon dioxide generated from the water isocyanate reaction series can be used to influence the density of the material by generating a cellular structure.

Polyurethanes with a high concentration of urea linkages in the hard phase tend to be strong elastomers with good flex lives.

The carbon dioxide generated as a by-product of the isocyanate-water-isocyanate reaction series can be employed to generate a cell structure in the material. With the use of a surfactant, the size and porosity of this cell structure can be controlled. The manufacturing control over the pore size of the material has important implications in the application of the article. In cell growth technology the pore sizes can be modified to accommodate cells and modify the cell to surface ratio.

The level of water used in the reaction determines the amount of carbon dioxide generated and the hard segment content of the polymer. The amount of carbon dioxide generated plays an important role in the density of the polyurethane. By this invention, the density can be controlled independently of the hard segment content by controlling the pressure of the reaction/forming chamber. Thus, biostable polyurethanes of this invention can be manufactured with densities

ranging from 15kg/m^3 to 1200kg/m^3 virtually independent of the hard segment content. Low density articles used in medical applications are desirable since the wrapping profile of the article is reduced and the delivery device profile is minimised, giving rise to a wider range of applications.

The polymerisation of biostable polyurethanes of this invention involves the reaction of -OH groups from the polyol with -NCO groups from the diisocyanate to form urethane linkages. These chemical groups are reacted in approximately equivalent ratios for the generation of linear polymers and with slight excess for a crosslinked (three-dimensional) molecular structure.

For the generation of biostable foams, water is used as the primary chain extender. Secondary chain extenders may be employed to alter the hard segment content or to alter specific properties. Manufacturing foams of the lowest densities per this invention is carried out by a combination of a water blown reaction, in a depressurised reactive/forming vessel and the incorporation of a physical blowing agent into the formulation. Secondary chain extenders can be either diamine, diol or alkanol amine based and should have a functionality of two or greater. Diol chain extenders are preferred.

Most diols or diamines make suitable chain extenders. Examples of such chain extenders include, ethylene glycol, 1,4 butanediol, diethylene glycol, triethylene glycol, 1,2 propane diol, 1,3 propane diol, 1,5 pentane diol, ethylene diamine, 1,4 diaminobutane, 1,6 diaminohexane, 1,7 diaminoheptane, 1,8 diaminooctane, and 1,5 diaminopentane.

Depending on the specific isocyanate reactive compounds used, the use of catalysts may be preferred or not. Using polyols as isocyanate reactive compounds, it is preferred to use catalysts for urethane formation. Catalysts for polyurethane formation that may be used are compounds, which promote the reaction between isocyanate and hydroxyl groups.

Such catalysts are widely available in the marketplace and include organic and inorganic salts of bismuth, lead, tin, iron, antimony, cadmium, cobalt, aluminum, mercury, zinc, cerium, molybdenum, vanadium, copper, manganese and zirconium, as well as phosphines and tertiary amines.

Tertiary amines are an important class of catalyst in which the nitrogen atom is not directly attached to an aromatic ring. Examples of tertiary amines are: triethylamine, N,N,N',N'-tetramethylenediamine, N-N,N',N'-tetramethyl-1,3-butanediamine, bis-2-dimethylaminoethyl ether, N,N-dimethylcyclohexylamine, N,N-dimethylbenzylamine, N-methylmorpholine, N-ethylmorpholine, 1,4–diazabicyclo-[2.2.2] octane and the like.

Biostable articles of this invention can be chemically prepared via the following methods:

The one shot process in which the diisocyanate, the polyol and the chain extender are mixed and reacted in one step.

The prepolymer method wherein an isocyanate-terminated prepolymer is first prepared and then the system is chain extended. An experienced person knowing the isocyanate content of the isocyanate composition and the functionality and molecular weight of the isocyanate- reactive compound, can calculate the relative amounts of reactants to be delivered to the reaction vessel in order to provide a prepolymer having any desired NCO content.

The quasiprepolymer system wherein some of the polyol is reacted with the isocyanate to generate an isocyanate terminated prepolymer in an excess of isocyanate. The remaining polyol and chain extenders are subsequently added to facilitate chain extension.

Biostable articles of this invention may be processed by any of the following techniques:

- Reactive blow moulding process, wherein the chemical ingredients for this invention are fed though two or three lines to a mixing head where it is

aggressively mixed and dispensed into a mould and chain extension and blowing reactions occur simultaneously. This process is suitable for the manufacture of a three dimensional molecular structure and is suited to the manufacture of low density porous and non-porous articles. The shot size used in this invention is 0.5g to 10g producing a three dimensional low density porous foam.

- Reactive moulding process, wherein the chemical ingredients are mixed and dispensed into a mould wherein chain extension occurs. This process is primarily suitable for the manufacture of three a three dimensional molecular structure and is suited to the manufacture of solid biostable articles.
- Reactive blowing process, wherein the chemical ingredients are aggressively mixed and dispensed in a continuous fashion and expand and chain extend simultaneously to form a continuous block of foam which is subsequently cut or machined into useful shapes. This process is suitable for the manufacture of a three dimensional molecular structure and is suited to the manufacture of low density porous and non-porous articles.

The article may be used as a cell scaffold to provide a substratum to promote the growth of adherent cell lines. Cells may be seeded onto the material, attach to the cell scaffold and replicate in a physiologically suitable environment. The nature of the article provides a large surface: area ratio, to enable cells infiltrate the material. The nature of the 3 dimensional material also allows the diffusion of nutrients and oxygen into the media and the diffusion of waste metabolites and carbon dioxide gas to leach from the three dimensional structure of the article. The cells can also secrete proteins as determined by the genetic make up of the cell.

As a result of the open cell structure of the material, cell – cell interactions can take place forming the basis of tissue formation.

This article has a number of applications in the field of cell growth/tissue engineering not limited to

- The use of the article as an implantable medical device to promote the growth of new tissues.
- The use of the article seeded with a specific cell type, implanted to promote the growth of new tissues.
- The use of the article in *in vitro* cell culture technologies and related applications.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

Claims

1. A biostable polyether polyurethane article comprising a medical implant and or a substratum for tissue and/or cell growth formed from an organic diisocyanate, a polyether polyol, a chain extender and a blowing agent.

2. A biostable polyether polyurethane article as claimed in claim 1 wherein the blowing agent is water.

3. A biostable polyether polyurethane article according to claim 1 or 2, wherein the density of the article is less than 1200kg/m^3.

4. A biostable polyether polyurethane article according to claim 1 or 2, wherein the density of the article is less than 200kg/m^3.

5. A biostable polyether polyurethane article according to any preceding claim wherein the ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyether polyurethane biomaterial.

6. A biostable polyether polyurethane article according to any preceding claim wherein the article is processed by a metering and mixing process, wherein the chemical components are aggressively mixed and dispensed into a vessel and chain extension and blowing reactions occur substantially simultaneously.

7. A biostable polyether polyurethane article according to claim 6 wherein the article is processed by a reactive moulding process, wherein the chemical components are mixed and dispensed into a vessel wherein chain extension occurs.

8. A biostable polyether polyurethane article according to claim 6 to wherein the article is processed in two stages, a first stage involving a reaction process in which the number of isocyanate linkages in the reaction vessel is approximately equal to the number of active hydrogens in the vessel.

9. A biostable polyether polyurethane article according to claim 6 wherein the article is processed by a reactive blowing process, in which the chemical components are aggressively mixed and dispensed substantially continuously and expand and chain extend substantially simultaneously to form a continuous block of foam which is subsequently cut or machined into a desired geometry.

10. A biostable polyether polyurethane article in any of claims 6 to 9 wherein the density of the said article is controlled by controlling the pressure in the reaction vessel.

11. A biostable polyether polyurethane article as claimed in any preceding claim having a pore size of from 10 microns to 900 microns.

12. A biostable polyether polyurethane article according to claim 11 having a pore size of between 35 microns to 200 microns.

13. A biostable polyether polyurethane wherein the urea linkages are derived from a water isocyanate reaction present in the hard segment phase.

14. A biostable polyether polyurethane wherein the percentage of urea linkages in the hard segment phase is greater than 0.5%.

15. A biostable polyether polyurethane wherein biuret linkages exist in the hard segment phase.

16. A biostable polyether polyurethane wherein aliphatic linkages exist in the hard segment phase.

17. A biostable polyether polyurethane article as claimed in any preceding claim, in which the isocyanate is selected from p-phenylene diisocyanate, tetramethylene diisocyanate, cyclohexane 1, 2-diisocyanate, m-tetramethylxylene diisocyanate, hexamethylene diisocyanate, 2,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate,, 4,4 -dicyclohexylmethane diisocyanate, 4,4, diphenylmethane diisocyanate, or mixtures thereof, especially with a triisocyanate.

18. A biostable polyether polyurethane article according to claim 17, in which the isocyanate is selected from 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, 4,4 -dicyclohexylmethane diisocyanate or mixtures thereof.

19. A biostable polyether polyurethane article according to claim 18 in which the isocyanate is 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane or 4,4 -dicyclohexylmethane diisocyanate and mixtures thereof.

20. A biostable polyether polyurethane article as claimed in any preceding claim wherein said article is prepared from a polyether urethane urea formed by the reaction of an aliphatic, aliphatic-alicyclic, aromatic, or aromatic-aliphatic diisocyanate or mixtures of said organic diisocyanate and a polyether polyol having a functionality of 2 or greater.

21. An article as claimed in claim 20 wherein the polyether polyol is of the formula

$HO - [R_1-O]_n-H$

where R_1 represents a linear hydrocarbon chain of from 2 to 16 carbon atoms and wherein n has a value greater than 2.

22. A biostable polyether polyurethane article of claim 21 wherein the polyether is a polyalkylene ether wherein the molecular weight is from 300 to 6000 molecular weight units.

23. A biostable polyether polyurethane article as claimed in claim 22 wherein the molecular weight is from 600 to 3000 molecular weight units.

24. A biostable polyether polyurethane article according to claim 21 or 22 wherein the polyol is selected from one or more of polyethylene glycol, polypropylene glycol, polydiethylene-ether glycol or polycaprolactone glycol.

25. A biostable polyether polyurethane article as claimed in claim 21 or 22 wherein the polyether polyols are polytetramethylene ether glycols.

26. A biostable polyether polyurethane article of claim 25 wherein the polytetramethylene ether glycols have a molecular weight of from 150 to 6000 molecular weight units.

27. A biostable polyether polyurethane article of claim 26 wherein the polytetramethylene ether glycols have a molecular weight of from 300 to 3000 molecular weight units.

28. A biostable polyether polyurethane article as claimed in any preceding claim formed from a prepolymer composition having an average functionality (n) of from 1.5 to 5.

29. A biostable polyether polyurethane article as claimed in any preceding claim wherein the chain extender is selected from a diol, a diamine, an alkanol amine, water or mixtures thereof.

30. A biostable polyether polyurethane article as claimed in claim 29 wherein the diol is an aliphatic diol having 2 to 10 carbon atoms.

31. A biostable polyether polyurethane article as claimed in claim 29 wherein the diamine is an aliphatic diamine having 2 to 10 carbon atoms.

32. A biostable polyether polyurethane article as claimed in claim 29 wherein the alkanol amine is an aliphatic alkanol amine having from 2 to 10 carbon atoms.

33. A biostable polyether polyurethane article as claimed in claim 29 or 30 wherein the aliphatic diol chain extender is selected from ethylene glycol, 1,4 butanediol, diethylene glycol, triethylene glycol, 1,2 propane diol, 1,3 propane diol, 1,5 pentane diol, isomers or mixtures thereof.

34. A biostable polyether polyurethane article as claimed in claim 29 or 33 wherein the aliphatic diamine chain extender is selected from ethylene diamine, 1,4 diaminobutane, 1,6 diaminohexane, 1,7 diaminoheptane, 1,8 diaminooctane, 1,5 diaminopentane, isomers or mixtures thereof.

35. A biostable polyether polyurethane article as claimed in claim 29 or 34 wherein the aliphatic alkanol amines chain extender is triethanolamine.

36. A biostable polyether polyurethane article as claimed in any preceding claim including a diol, a diamine and/or an alkanol amine as a second chain extender.

37. A biostable polyether polyurethane article according to claim 36 wherein the second chain extender is an aliphatic diol having from 2 to 10 carbon atoms.

38. A biostable polyether polyurethane article according to claim 36 wherein the second chain extender is an aliphatic diamine having 2 to 10 carbon atoms.

39. A biostable polyether polyurethane article according to claim 36 wherein the second chain extender is an aliphatic alkanol amine having from 2 to 10 carbon atoms.

40. A biostable polyether polyurethane article according to any preceding claim wherein the article is a medical implant.

41. A biostable polyether polyurethane article according to claim 40 wherein the article is a septal defect occluder, a vessel occluder, a vessel defect occluder, a mammary prosthesis, a muscle bulking agent, a gynaecological implant or, an embolic filter.

42. A biostable polyether polyurethane article as claimed in any of claims 1 to 36 wherein the article is a substratum for tissue and/or cell growth.

43. An article as claimed in claim 42 comprising a cell matrix for cell growth technologies, tissue repair and in drug delivery applications.

44. A method for manufacturing a biostable polyether polyurethane article as claimed an any preceding claim comprising reacting an organic diisocyanate, a polyether polyol and a diol, diamine or water chain extender.

45. A method as claimed in claim 44 wherein the components are issued and dispersed into a reaction vessel in which chain extensions and blowing reactions occur substantially simultaneously.

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46. A method as claimed claim 45 wherein the pressure in the reaction vessel is controlled by controlling the pressure in the reaction vessel.

Abstract

A biostable polyether polyurethane article comprises a medical implant and or a substratum for tissue and/or cell growth formed from an organic diisocyanate, a polyether polyol, a chain extender and a blowing agent. The density of the biostable polyether polyurethane article is less than 200kg/ m^3. The ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyether polyurethane biomaterial.